ARTICLE

Economic Analysis: Randomized Placebo-Controlled Clinical Trial of Erlotinib in Advanced Non–Small Cell Lung Cancer

Penelope A. Bradbury, Dongsheng Tu, Lesley Seymour, Pierre K. Isogai, Liting Zhu, Raymond Ng, Nicole Mittmann, Ming-Sound Tsao, William K. Evans, Frances A. Shepherd, Natasha B. Leighl, on behalf of the NCIC Clinical Trials Group Working Group on Economic Analysis

Correspondence to: Natasha B. Leighl, MD, MMSc, FRCPC, 5-105 610 University Ave, Toronto, ON, Canada M5G 2M9 (e-mail: natasha.leighl@uhn.on.ca).

Background   The NCIC Clinical Trials Group conducted the BR.21 trial, a randomized placebo-controlled trial of erlotinib (an epidermal growth factor receptor tyrosine kinase inhibitor) in patients with previously treated advanced non–small cell lung cancer. This trial accrued patients between August 14, 2001, and January 31, 2003, and found that overall survival and quality of life were improved in the erlotinib arm than in the placebo arm. However, funding restrictions limit access to erlotinib in many countries. We undertook an economic analysis of erlotinib treatment in this trial and explored different molecular and clinical predictors of outcome to determine the cost-effectiveness of treating various populations with erlotinib.

Methods   Resource utilization was determined from individual patient data in the BR.21 trial database. The trial recruited 731 patients (488 in the erlotinib arm and 243 in the placebo arm). Costs arising from erlotinib treatment, diagnostic tests, outpatient visits, acute hospitalization, adverse events, lung cancer–related concomitant medications, transfusions, and radiation therapy were captured. The incremental cost-effectiveness ratio was calculated as the ratio of incremental cost (in 2007 Canadian dollars) to incremental effectiveness (life-years gained). In exploratory analyses, we evaluated the benefits of treatment in selected subgroups to determine the impact on the incremental cost-effectiveness ratio.

Results   The incremental cost-effectiveness ratio for erlotinib treatment in the BR.21 trial population was $94 638 per life-year gained (95% confidence interval = $52 359 to $429 148). The major drivers of cost-effectiveness included the magnitude of survival benefit and erlotinib cost. Subgroup analyses revealed that erlotinib may be more cost-effective in never-smokers or patients with high *EGFR* gene copy number.

Conclusion   With an incremental cost-effectiveness ratio of $94 638 per life-year gained, erlotinib treatment for patients with previously treated advanced non–small cell lung cancer is marginally cost-effective. The use of molecular predictors of benefit for targeted agents may help identify more or less cost-effective subgroups for treatment.

J Natl Cancer Inst 2010;102:298–306

Lung cancer is the leading cause of cancer-related death and imposes a considerable public health burden across the world (1). In Canada in 1998, it was estimated that the cost arising from lung cancer–related hospital care and mortality costs was $3.0 billion (Canadian dollars) (2). Estimates from the United States indicate that the cost of treating each lung cancer patient has increased by more than a factor of five from 1991 to 2002 (3). These costs may increase even more with the development of novel targeted therapies for lung cancer.

Non–small cell lung cancer (NSCLC) accounts for 85% of all primary lung cancers. The disease frequently presents in an advanced stage when cure is not possible, and treatment intent is palliative. First- and second-line chemotherapy is the standard of care for patients who have advanced NSCLC and a good performance status; such therapy has improved symptom control and survival benefits compared with best supportive care (4–6). After chemotherapy has failed, the only treatment shown to provide additional quality of life and survival benefit is the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib (7,8).

The NCIC Clinical Trials Group undertook an international, randomized, placebo-controlled trial of erlotinib after the failure of first- or second-line chemotherapy, the BR.21 trial (NCT00036647, http://www.clinicaltrials.gov) (7). This landmark trial enrolled patients between August 14, 2001, and January 31, 2003, and was the first to demonstrate an advantage for an EGFR tyrosine kinase inhibitor in overall survival and in quality of life (7,8). Funding restrictions in many countries limit a patient's access to erlotinib; therefore, an accurate evaluation of the cost-effectiveness of erlotinib is important if patients are to have access to this therapy in publically funded health systems.

The BR.21 trial found a median overall survival benefit of 2 months for patients in the erlotinib arm compared with the placebo arm (adjusted hazard ratio [HR] = 0.70, $P < .001$). Higher response rates with erlotinib were observed in some groups (eg, patients of Asian origin, women, never-smokers, and patients with adenocarcinoma). However, among erlotinib-treated patients, never-smoking status was the only statistically significant clinical predictive factor for improved overall survival in multivariable analysis. Molecular predictors of outcome, including EGFR protein expression status, *EGFR* gene mutation status, increased *EGFR* gene copy number, and *KRAS* gene mutation status, were also evaluated when tissue was available to determine whether any of these molecular markers alone or in combination would be useful in selecting patients with a higher probability of benefiting from erlotinib treatment (9,10).

We undertook an economic analysis of erlotinib treatment in this trial and explored different molecular and clinical predictors of outcome to determine the cost-effectiveness of treating various populations with erlotinib. The primary objective of this retrospective analysis was to determine the incremental cost-effectiveness ratio, as measured in cost per life-year gained, of erlotinib treatment in patients with advanced NSCLC after failure of chemotherapy, by use of individual patient data from the BR.21 trial. As a secondary objective, and in an exploratory analysis, we evaluated the impact of both clinical and molecular predictors of outcome and the line of therapy on the incremental cost-effectiveness ratio of erlotinib treatment.

Patients and Methods

This study was a retrospective analysis of the direct medical costs associated with erlotinib treatment in the BR.21 trial from the perspective of the Canadian public health-care system. Resource utilization was obtained from the database of a prospective clinical trial that included data from all 731 patients in the study, who were from Canadian and international centers, with 488 patients in the erlotinib arm and 243 in the placebo arm. Patients received either 150 mg of erlotinib or placebo orally each day until development of disease progression or unacceptable toxicity. Dose reductions were permitted for treatment toxicity, such as severe rash or diarrhea that could not be controlled with supportive measures. Costs were determined at the Princess Margaret Hospital–University Health Network, by use of the 2007 Schedule of Benefits and Fees from the Ontario Health Insurance Plan, unless otherwise stated (11). Investigators collecting resource utilization data and costs (P. A. Bradbury, N. B. Leighl, and R. Ng) were blinded to patient treatment arm. Costs were derived in 2007 Canadian dollars. All non-2007 costs were adjusted to 2007 costs by use of the Canadian Price Adjustment Index for Health and Personal Cares (www.bankofcanada.ca). Because the median survival time in the study was less than 1 year and because very few patients remained on study at 18 months in both arms (7), discounting was not used. Resource utilization data collected during the study horizon were used in this analysis as they were monitored and verified through source documentation. It was assumed, given the short survival of end-stage NSCLC patients with no further therapeutic options associated with a proven overall

CONTEXT AND CAVEATS

Prior knowledge
The randomized placebo-controlled BR.21 trial evaluated erlotinib (an epidermal growth factor receptor tyrosine kinase inhibitor) vs placebo treatment in patients with previously treated advanced non–small cell lung cancer. This trial observed a statistically significant median overall survival benefit of 2 months for patients in the erlotinib arm compared with the placebo arm.

Study design
An economic analysis of erlotinib treatment in this trial explored different predictors of outcome to determine the cost-effectiveness of treating various populations with erlotinib and to calculate the incremental cost-effectiveness ratio.

Contribution
Erlotinib treatment had an incremental cost-effectiveness ratio of $94 638 per life-year gained, with major drivers of cost-effectiveness being the magnitude of survival benefit and the cost of erlotinib. In subgroup analyses, erlotinib appeared to be more cost-effective in never-smokers and in patients with high *EGFR* gene copy number.

Implications
Erlotinib treatment for patients with previously treated advanced non–small cell lung cancer is marginally cost-effective. The use of molecular predictors of benefit for targeted agents may help identify more or less cost-effective subgroups for treatment.

Limitations
Some costs were not captured in the database and required modeling. Prospective utility data were not collected in the BR.21 trial.

From the Editors

survival benefit, that patients stopping study treatment because of disease progression with an expected short survival duration would incur similar palliative care costs in both arms of the trial. A minority of patients (18% in the erlotinib arm and 21% in the placebo arm) received additional systemic therapy after discontinuing the clinical trial. These proportions were similar in both arms and therefore not included in the analysis, given the unlikely impact on incremental cost.

Drug Costs

Information on doses and the duration of study drug administration was obtained directly from the trial database. Current costs for erlotinib in 2007 Canadian dollars were obtained from PPS Pharma Publication (Total Pricing Systems, Inc, New Brunswick, CA) (12).

Hospitalization and Serious Adverse Events

The number of inpatient hospital days for each patient was obtained from the trial database while they were included in the study. We used the World Health Organization, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Version for 2007, Code (ICD-10), to assign the most responsible diagnosis on the basis of the serious adverse event narrative review (13). Costs per diem were obtained from the

Ontario Case Costing Acute Inpatient Database. Costs attributed to investigations in the Ontario Case Costing Acute Inpatient Database figures were removed to avoid double counting. Instead, costs for investigations were derived from individual patient data in the BR.21 trial database. Complex admissions with multiple diagnoses (approximately 10%) were reviewed by two investigators (N. B. Leighl and P. A. Bradbury), with 100% concordance on diagnostic codes and attributed costs. The 36 hospitalizations that did not have adequate accompanying information to enable accurate assessment of resource utilization were not included in this analysis. There was no imbalance between the number of patients (P = .15) and the length of hospital stay (P = .7) across the two arms for the hospitalizations that were excluded.

Emergency room visits were not routinely captured in the database, but their costs were determined when listed in the serious adverse event narrative. The costs arising from lung cancer patients who visited University Health Network emergency departments have been described previously (14) and were adjusted to 2007 costs.

Diagnostic Tests and Procedures
Data on blood tests, imaging, and cardiac testing were taken from the trial database. Procedures (eg, thoracocentesis) were not captured systematically in the database but were assumed to be similar in both arms.

Concomitant Medications
Medication use for symptom management and erlotinib therapy were captured from the trial database. Costs for the use of analgesic agents, antibiotics, antinauseant agents, steroid drugs, anticoagulant agents, and growth factors were modeled on the basis of current Canadian practice. Duration of treatment was derived from the trial database. Costs for managing treatment-related toxicity were attributed to patients on the basis of reported toxicities in the trial database (eg, rash or stomatitis). From expert opinion (F. A. Shepherd, N. B. Leighl, G. Liu, and R. Burkes) and published literature (15,16), it was conservatively assumed that the majority of patients experiencing a rash with a grade 2 or higher would receive 7 days of oral macrolide antibiotic therapy and hydrocortisone lotion. Medications costs were obtained from Princess Margaret Hospital pharmacy. Costs that were modeled for management of toxic effects were cross-referenced with the concomitant medication database to avoid double counting.

Transfusions
The costs of transfusions (ie, blood per unit and platelets per 5 U) were obtained from the Canadian Blood Services (14) and adjusted to 2007 costs by use of the Canadian Price Adjustment Index for Health and Personal Cares. Administration costs included hotel, nursing, and laboratory costs.

Radiation Therapy
Information on radiation therapy was obtained from the trial database. If the radiation doses captured were nonstandard, a radiation oncologist (K. Franks, who was blinded to treatment arm) reviewed and recommended standard dose and fractionation schemes that would reflect Canadian practice. Radiation costing

included cost per fraction and treatment review costs (14) but excluded computed tomography planning, which is not standard Canadian practice for palliative treatment.

Outpatient and Physician Costs
Outpatient visits were obtained from the trial database. All medical oncology visits were costed as follow-up visits. Radiation therapy outpatient visits were classified as an initial consultation and one treatment review visit for each week of radiation therapy that contained more than five fractions. The cost of visits included hotel costs (overhead; administration; facilities including maintenance, housekeeping, porter supplies, medical records, and equipment), staff salaries, and physician billings. The salary costs included benefits, educational leave, and hours attributed to the lung cancer clinic (14). The total cost was averaged over the number of outpatient visits.

Molecular Analyses in BR.21 Clinical Trial
Molecular predictors evaluated in subgroup analyses included EGFR protein expression by immunohistochemistry by use of Dako EGFR PharmDx kits (Dako, Carpinteria, CA). Tumors were considered to be positive for EGFR when more than 10% of tumor cells demonstrated partial or complete membranous staining of any intensity (from 322 patients) (9,10). *EGFR* mutation status was determined by polymerase chain reaction amplification of exons 18 through 21 of the *EGFR* gene (from 204 patients). *EGFR* gene copy number was determined by fluorescence in situ hybridization, and tumors were classified as positive for fluorescence in situ hybridization if they had a high degree of polysomy or amplification (from 159 patients). *KRAS* mutations were identified by polymerase chain reaction amplification and sequencing of exon 2 of the *KRAS* gene (from 106 patients) (9,10). Results from the molecular univariate analyses demonstrated a statistically significant overall survival benefit for patients with tumoral EGFR protein expression (HR of death = 0.68, 95% confidence interval [CI] = 0.49 to 0.95, P = .02), high *EGFR* copy number (HR of death = 0.43, 95% CI = 0.23 to 0.78, P = .004), and wild-type *KRAS* (HR of death = 0.69, 95% CI = 0.49 to 0.97, P = .311) but not for patients with low *EGFR* copy number (HR of death = 0.80, 95% CI = 0.49 to 1.29, P = .353), EGFR-activating mutations (HR of death = 0.55, 95% CI = 0.25 to 1.19, P = .122), patients with *KRAS* mutations (HR of death = 1.67, 95% CI = 0.62 to 4.50, P = .310), or negative EGFR protein expression (HR of death 0.93, 95% CI = 0.63 to 1.36, P = .70). In addition, clinical predictors of response including female sex, Asian ethnicity, adenocarcinoma histology, and never-smoking status were associated with an increased responsiveness to erlotinib. Never-smoking status was the only clinical predictor to be associated with an overall survival benefit (7). We postulated that clinical and molecular predictors of outcome could be used to identify patient subgroups for which erlotinib therapy was more cost-effective than an unselected population.

Statistical Analysis
All resources per patient were multiplied by cost per resource. Overall mean resource utilization and costs were calculated. The incremental cost was calculated as the incremental difference

between the mean overall cost of treatment per patient in the erlotinib arm compared with that in the placebo arm. The incremental effectiveness was the difference in the mean survival time (as estimated from the restricted mean of Kaplan–Meier curves) between the erlotinib and the placebo arms. The use of mean survival time is a standard measure in economic analysis (14,17) and preferred to median survival because it allows the required arithmetic manipulation of incremental survival to derive the incremental cost-effectiveness ratio. The mean overall survival was calculated with restriction to the longest observed survival time (ie, the horizon of the trial) and by the Kaplan–Meier method, which takes into account of survival times of patients censored (including those still alive at the end of the study). The incremental cost-effectiveness ratio was calculated as the ratio of incremental cost (in 2007 Canadian dollars) to incremental effectiveness (in life-years gained). One-way sensitivity analyses used clinically relevant and pragmatic ranges. Bootstrap methodology with 1000 replicates was used to calculate the 95% confidence intervals and to construct the cost-effectiveness acceptability curve (18). Sensitivity analysis was conducted by varying the major drivers of cost, study drug, and incremental survival, by 20% and two standard deviations (SDs).

Exploratory subgroup analyses were performed to evaluate the impact of clinical (sex, smoking status, histology, ethnicity, and number of previous treatments) and molecular predictors of outcome (EGFR protein expression status, *EGFR* tyrosine kinase mutation status, *EGFR* gene copy number, and *KRAS* gene mutation status) on the incremental cost-effectiveness ratio. Because this was an exploratory analysis and because these tests are not currently routine part of clinical practice, costs that would be incurred from conducting these additional analyses was not included in the primary cost analysis. Furthermore, the costs of immunohistochemistry for EGFR protein expression status, fluorescence in situ hybridization for *EGFR* gene copy number, and mutation analysis for *EGFR* tyrosine kinase status and *KRAS* gene mutation status were undertaken on samples from patients on both arms of the study and therefore would not alter the incremental cost. All statistical tests were two-sided.

Results

Patient Characteristics and Survival Data

Of 731 patients recruited for the trial, 488 previously treated patients were randomly assigned to receive erlotinib treatment and 243 were randomly assigned to receive placebo (ratio for randomization = 2:1) (7). At the time of study analysis, 682 patients had had progressive disease and 587 deaths had occurred. The median overall survival was 6.7 months (SD = 0.56 years) in the erlotinib arm and 4.7 months (SD = 0.39 years) in the placebo arm (difference = 2 months; HR = 0.70, P < .001). The mean overall survival was 9.0 months (SD = 0.75 years and standard error [SE] = 0.03) in the erlotinib arm and was 7.4 months (SD = 0.62 years and SE = 0.04) in the placebo arm (difference = 1.6 months).

Resource Utilization and Costs

The mean resource utilization for treatment, outpatient visits, hospitalization, transfusions, and radiation is summarized in Table 1. Resource utilization between Canada and other participating

Table 1. Mean resource utilization among patients randomly assigned to the erlotinib arm (n = 488) or to the placebo arm (n = 243)*

Mean resource utilization	Erlotinib arm	Placebo arm
Duration of treatment, wk (SD)	14.4 (14.3)	12.0 (10.3)
Outpatient visits, No. (SD)	6.0 (4.5)	4.6 (3.2)
Duration of acute hospitalization, d (SD)	3.7 (8.9)	3.3 (8.9)
Radiation therapy, No. of fractions (SD)	0.4 (2.4)	0.7 (2.9)
Red blood cell transfusions, No. of units (SD)	0.2 (1.0)	2.3 (0.5)

* All patients in the erlotinib arm and the placebo arm were included in the calculation of the means.

countries was similar (data not shown); therefore, all patients recruited to the BR.21 trial were included in this economic analysis, and Canadian costs were assigned. When we determined mean costs per patient for erlotinib (treatment arm only), investigations, outpatient and hospital visits, physician fees, concomitant medications, radiation therapy, and transfusions (Table 2), erlotinib was found to be the main driver of cost (71%), followed by hospitalization (15% in the erlotinib arm). Hospitalization was the major cost driver in the placebo group (61%). Costs for radiation therapy were greater in the placebo arm than in the erlotinib arm.

Incremental Cost-effectiveness Ratio

The mean cost per patient was $16 487 in the erlotinib arm and $4184 in the placebo arm. The mean incremental survival difference between the two arms was 0.13 years, in favor of the erlotinib arm. This difference resulted in an incremental cost-effectiveness ratio for erlotinib in patients with advanced previously treated NSCLC of $94 638 (in 2007 Canadian dollars; 95% CI = $52 359 to $429 148) per life-year gained. The associated cost-effectiveness acceptability curve, which summarizes the probability of erlotinib being cost-effective compared with best supportive care at a given threshold of interest, is shown in Figure 1.

Sensitivity Analysis

Sensitivity analysis was performed by varying the cost of erlotinib plus or minus 20% and the incremental survival difference by two standard deviations (Figure 2). Varying the cost of erlotinib resulted in an incremental cost-effectiveness ratio of $77 547 to $114 190 (2007 Canadian dollars). The magnitude of the survival benefit was the main driver of the cost-effectiveness ratio; thus, the incremental cost-effectiveness ratio was most sensitive to changes in overall survival, ranging from $55 386 to $356 173 per life-year gained (2007 Canadian dollar). However, a variation by two standard deviations in survival benefit is highly unlikely; thus, we expected the range of cost-effectiveness is expected to remain in the range of the mean point estimate (ie, $94 638).

Incremental Cost-effectiveness Ratio of Subgroups as Defined by Predictors of Outcome

We evaluated the impact of clinical and molecular predictors of outcome on cost-effectiveness through subgroup analyses (Table 3). Never-smoking status and *EGFR* gene copy number had

Table 2. Mean treatment costs per patient (2007 Canadian dollars) among patients randomly assigned to the erlotinib arm (n = 488) or to the placebo arm (n = 243)*

Component	Mean cost per patient with component (SD)		Incremental mean cost ($)
	Erlotinib arm	**Placebo arm**	
Erlotinib	$11 756 ($11 697)	$0.0	+$11 756
Diagnostic tests	$1056 ($722)	$837 ($474)	+$219
Outpatient visits	$623 ($473)	$477 ($334)	+$146
Concomitant medications†	$307 ($1341)	$159 ($491)	+$148
Management of treatment-related toxicity‡	$70 ($102)	$6.0 ($22)	+$64
Hospitalizations	$2525 ($6541)	$2562 ($7361)	−$37
Radiation therapy	$69 ($377)	$109 ($463)	−$40
Red blood cell transfusions	$79 ($353)	$34 ($172)	+$45

* All patients in the erlotinib arm and the placebo arm were included in the calculation of the means.

† Non–small cell lung cancer–related medications.

‡ Medical therapy for grade 2 or greater diarrhea, rash, nausea or vomiting, stomatitis, dehydration, and anorexia.

the greatest impact on incremental cost-effectiveness ratio values, identifying subsets of patients for whom erlotinib therapy has an associated incremental cost-effectiveness ratio of less than $40 000 per life-year gained. Adenocarcinoma histology and EGFR protein expression status were also associated with a lower incremental cost-effectiveness ratio, but female sex and *EGFR* gene mutation status were associated with higher incremental cost-effectiveness ratios. These results may reflect the high response rate to erlotinib in these subgroups without a corresponding statistically significant improvement in overall survival. Finally, erlotinib treatment in the second-line setting ($67 844) appeared more cost-effective than in the third-line setting ($110 411). This difference resulted from the larger mean survival difference between patients who were treated with erlotinib in the second-line setting and those who were treated in the third-line setting.

Discussion

In this analysis of the NCIC Clinical Trials Group BR.21 randomized trial, the incremental cost-effectiveness ratio for erlotinib therapy in previously treated advanced NSCLC patients was found to be $94 638 per life-year gained (2007 Canadian dollars). We believe that these data can be generalized to other jurisdictions because resource utilization was similar among the different countries participating in the trial. The major driver of cost in this analysis was erlotinib drug cost, and incremental survival gain was the major driver of the incremental cost-effectiveness ratio. Drug costs may have differed somewhat between regions but were largely similar. Much of the additional resource utilization observed in this trial would be standard in the management of any advanced pretreated lung cancer patient. Although these costs may differ between countries, usually these differences are not large. Finally, because there is evidence that some subgroups of patients may derive greater benefit from erlotinib, we undertook exploratory analyses to define the impact of predictors of outcome on the cost-effectiveness of erlotinib.

Despite the statistically significant, albeit modest, overall survival and quality-of-life benefits from erlotinib in this population, many jurisdictions have chosen not to fund erlotinib therapy for reasons of cost. For example, the National Institute for Health and Clinical Excellence (United Kingdom) initially declined to fund
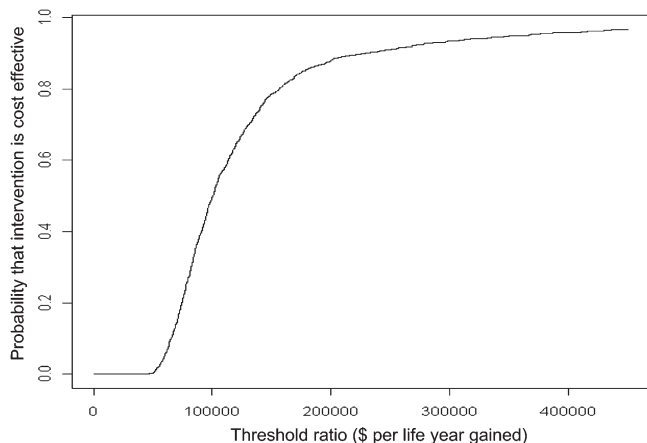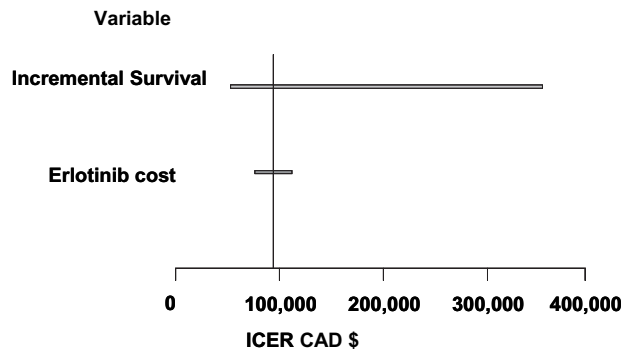
Figure 1. Cost-effectiveness acceptability curve. This curve summarizes the probability that erlotinib is cost-effective compared with best supportive care at a given threshold value. Cost was measured in 2007 Canadian dollars.

ICER= incremental cost effectiveness ratio

Figure 2. Tornado plot of sensitivity analysis of incremental cost-effectiveness ratio (ICER). Sensitivity analysis is presented with incremental survival varied by plus or minus 2 SDs and with the cost of erlotinib varied by plus or minus 20%. Cost was measured in 2007 Canadian dollars.

Table 3. Incremental cost-effectiveness ratio (ICER) for clinical and molecular subgroups (2007 Canadian dollar per life-years gained)*

Characteristic	No. of patients	ICER, $ per life-year gained (95% CI)
Sex		
Female	256	$120 671 (−$1 346 285 to $1 264 812)
Male	475	$96 601 (−$534 674 to $777 094)
Histology		
Adenocarcinoma	365	$75 059 ($43 454 to $338 913)
Nonadenocarcinoma	366	$239 978 (−$1 900 907 to $1 508 423)
Smoking status		
Never-smoker	146	$39 487 ($29 963 to $68 018)
Smoker (past or present)	545	$504 911 (−$3 149 228 to $3 112 895)
Ethnicity		
Asian	91	$83 181 (−$175 449 to $502 848)
Other	640	$109 380 (−$515 431 to $845 207)
No. of previous chemotherapy regimens		
1	364	$67 844 ($39 220 to $330 026)
2	357	$110 411 (−$816 326 to $1 245 117)
EGFR protein expression		
Positive	184	$63 805 ($30 102 to $297 301)
Negative	141	$469 003 (−$1 287 055 to $1 764 016)
EGFR gene mutation		
Exon 19 deletion and/or exon 21 L858R mutation	34	$138 168 (−$1 125 890 to $1 377 049)
Wild-type or other mutation	170	$87 994 (−$833 900 to $706 634)
KRAS gene mutation		
Mutation in codons 12 and 13	30	BSC dominant
Wild type	176	$76 657 (−$470 406 to $645 461)
EGFR gene copy number		
High	61	$33 353 (−$91 232 to $384 569)
Low	98	$109 792 (−$834 935 to $831 854)

* BSC = best supportive care; CI = confidence interval; EGFR = epidermal growth factor receptor.

erlotinib therapy but recently recommended erlotinib therapy as an alternative treatment to docetaxel chemotherapy, provided the manufacturer supplies the drug at a cost that ensures equivalence between erlotinib and docetaxel (19). The Pharmaceutical and Therapeutics Advisory Committee of New Zealand also has declined to fund erlotinib (20,21). The Pharmaceutical Benefits Advisory Committee in Australia rejected the initial application for erlotinib funding and only recently approved erlotinib with restrictions, similar to those within Canada (22,23). This highlights the challenge facing publicly funded health-care systems in absorbing the rising costs associated with new therapies.

To our knowledge, this is the first study to evaluate the cost-effectiveness of an EGFR tyrosine kinase inhibitor using clinical trial data. However, in a modeled decision analytic study, to determine the impact of introducing erlotinib therapy on US health-care expenditure, it was estimated (24) that erlotinib therapy would have a minimal impact on the overall annual health-care budget. This study estimated the cost of erlotinib therapy in the second- and third-line setting would be offset by savings in the second-line setting because of the favorable side effect profile and reduced administration costs compared with chemotherapy. In a second study to evaluate the incremental costs and quality-adjusted life-years of erlotinib, docetaxel, and pemetrexed from the US payer perspective, erlotinib was associated with reduced costs and appeared cost saving in a probabilistic sensitivity analysis (25). Pemetrexed was included in both models; funding for this drug is restricted by many public health-care systems because of its high cost (pemetrexed costs US $3998 per cycle; docetaxel costs US $2483 per cycle, and erlotinib costs US $2330 per month of treat-

ment) (24) and lack of any survival benefit compared with docetaxel in the second-line setting (5). Furthermore, erlotinib has not yet been shown to be equivalent to either pemetrexed or docetaxel in the second-line setting among patients with advanced NSCLC who are eligible for chemotherapy, although results of a comparative trial are pending. Another EGFR tyrosine kinase inhibitor, gefitinib, has demonstrated noninferiority compared with docetaxel in a randomized controlled trial as a second-line therapy (26), but a trial with a similar design that was conducted in Japan failed to demonstrate similar survival between the arms, perhaps because only 36% of patients proceeded to third-line chemotherapy compared with 53% who proceeded to third-line EGFR tyrosine kinase inhibitor after second-line chemotherapy (27). Thus, the sequencing of these agents may be important. We found the incremental cost-effectiveness ratio of erlotinib was lower in the second-line setting than in the third-line setting among patients who were not eligible to receive additional chemotherapy. However, as clinical trials evaluating erlotinib as an earlier treatment option and as a maintenance therapy (28) are conducted, additional economic analyses are required to determine the most cost-effective setting for EGFR tyrosine kinase inhibitors.

As targeted therapy evolves, it may be tailored to subgroups of patients who benefit preferentially from selected treatments, defined by molecular and/or clinical features. Of the clinical predictors of benefit, a lifetime nonsmoking history was associated with the lowest incremental cost-effectiveness ratio. Interestingly, female sex, which was associated with an increased response rate to EGFR tyrosine kinase inhibitors, was not associated with a lower incremental cost-effectiveness ratio. This result may reflect the

prognostic impact of sex and the higher incidence of *EGFR* gene mutations in women (7,29).

We found that patients with tumors that had a high *EGFR* copy number had a very favorable incremental cost-effectiveness ratio but that the presence of EGFR-activating mutations located in exon 19 or 21 was not associated with a lower incremental cost-effectiveness ratio. In the BR.21 trial, patients with EGFR-activating mutations who were randomly assigned to either the placebo or the erlotinib group lived longer than patients without activating mutations (HR = 0.55, 95% CI = 0.25 to 1.19) (9). However, the median survival difference between patients with activating mutations in the placebo arm and those with activating mutations in the erlotinib arm was only 2.6 months (median survival of 8.3 and 10.9 months, respectively). Patients with good prognostic features in both study arms appear to remain on treatment for longer periods of time. Therefore, the relatively small survival difference between treated and untreated patients with good prognosis corresponds to a higher incremental cost-effectiveness ratio, despite potential benefit from erlotinib. By contrast, patients in the placebo arm with a high *EGFR* copy number had a median overall survival of only 3.1 months and those in the erlotinib arm had a median overall survival of 10.5 months (HR = 0.42, 95% CI = 0.23 to 0.78) (9). The large incremental survival benefit with erlotinib treatment in this subgroup was associated with a favorable cost-effectiveness ratio in our study. Similarly, in a decision analytic model to explore the impact of testing for EGFR protein expression by immunohistochemistry or *EGFR* gene copy number, Carlson et al. (30) determined that gene copy number was the optimal testing strategy to select patients for erlotinib therapy. These results are clearly driven by the clinical data from the NCIC CTG BR.21 trial. We did not include the costs of performing the molecular tests in our analysis. These tests are not currently considered routine in many countries, and patients in both arms of the BR.21 trial had tumor samples tested; thus, there would be no incremental cost of testing in our exploratory analysis. However, if pharmacogenomic testing becomes part of routine practice, such testing would have a clear budget impact, not only for the cost of molecular testing but also for the need to repeat biopsy examinations in some patients when existing tumor sampling is insufficient for testing.

Initially, funding for therapy with an EGFR tyrosine kinase inhibitor in Australia was limited to patients whose tumors were known to carry *EGFR*-activating mutations (31). Although this strategy may appear to be minimize costs from the payer perspective because fewer patients would be treated overall, our results suggest that it may result in many patients being denied therapy who might otherwise benefit at an acceptable cost to society. Patients with *EGFR*-activating mutations are uncommon in North American and Western populations, with reported rates of 10% or less (29). The predictive value of *EGFR* mutations for survival benefit with EGFR tyrosine kinase inhibitors, as well as the economic impact of treating this group, will be best assessed through recent and ongoing trials in Asia, where the mutation rate is substantially higher. For example, a first-line study conducted in Asia that compared gefitinib with carboplatin or paclitaxel among never-smokers or former light smokers with advanced lung adenocarcinoma found improved progression-free survival in the gefitinib arm among patients whose tumors had *EGFR* mutations (32).

When comparing EGFR tyrosine kinase inhibitor therapy with chemotherapy, the predictive value of molecular markers may differ from the results observed in the BR.21 trial. In a randomized trial that compared gefitinib with docetaxel chemotherapy in the second-line setting, biomarkers were not associated with better overall survival in either the chemotherapy or the EGFR tyrosine kinase inhibitor treatment arm (26).

Our study has potential limitations associated with its design. Although the use of individual patient data minimized the need to model resource utilization, some costs were not captured in the database and did require modeling, which reflects the challenges of any retrospective analysis. These modeled costs were minor contributors to the final incremental cost-effectiveness ratio and were similar to those in other studies (24,25). Costs of care beyond the study timeline could not be captured reliably from the trial database and, thus, were not included in this analysis. However, erlotinib is a palliative treatment, and there is no other therapy that has been proven to improve outcome in the third-line setting. Combined with the short survival duration beyond progression in both study arms, it is reasonable to assume that resource utilization and costs off-study were similar in both arms. Because the trial enrolled patients at multiple sites worldwide, we investigated resource utilization among countries and found such utilization to be similar among countries. This result reflects similarities of practice for the management of the terminal phase of NSCLC when there is no additional systemic therapy of proven benefit and prognosis is poor. Finally, prospective utility data were not collected as part of the BR.21 trial.

In summary, erlotinib in previously treated patients with advanced NSCLC has an incremental cost-effectiveness ratio of $94 638 per life-years gained (2007 Canadian dollar). This figure exceeds the US threshold historically accepted as cost-effective (ie, $50 000 per quality-adjusted life-year) (33) and is at the upper boundary of moderate cost-effectiveness from a Canadian perspective (34, 36). Our analysis indicated that erlotinib was of marginal cost-effectiveness at best and was in the higher range of cost-effectiveness ratios that high-resource countries may consider acceptable. Thus, it may be possible to enhance the cost-effectiveness of this treatment through the clinical and molecular selection of patients for treatment. However, caution is required in interpreting data from these post hoc analyses that include small numbers of patients. Currently, most countries do not use biomarkers to guide selection of NSCLC patients for EGFR tyrosine kinase inhibitor therapy, and the best biomarkers may be differ between Asian and non-Asian populations. Although *EGFR* mutations may guide treatment decisions for use of EGFR tyrosine kinase inhibitors in Asia in the future, in particular decisions about the order in which EGFR inhibitors and chemotherapy should be given (30), this marker may be less valuable in North American and European populations, in which *EGFR* mutations are less common. Our data support the use of *EGFR* copy number as a biomarker to select a population with a more favorable cost-effectiveness ratio for erlotinib treatment.

Despite the challenges of identifying predictive biomarkers to guide treatment decisions, EGFR inhibitor therapy has become an important treatment for advanced NSCLC patients. The cost-effectiveness ratio of erlotinib therapy in an unselected advanced

NSCLC population is most sensitive to changes in incremental survival benefit and in erlotinib drug cost. Ongoing efforts to identify which patients are most likely to benefit from treatment and to make targeted cancer therapies more affordable will serve to make this important treatment option available for lung cancer patients worldwide.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* 2008;58(2):71–96.
2. Demeter SJ, Jacobs P, Chmielowiec C, et al. The cost of lung cancer in Alberta. *Can Respir J.* 2007;14(2):81–86.
3. Warren JL, Yabroff KR, Meekins A, Topor M, Lamont EB, Brown ML. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst.* 2008;100(12):888–897.
4. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol.* 2000;18(10):2095–2103.
5. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol.* 2004;22(9):1589–1597.
6. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ.* 1995;311(7010):899–909.
7. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* 2005;353(2):123–132.
8. Bezjak A, Tu D, Seymour L, et al. Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol.* 2006;24(24):3831–3837.
9. Zhu CQ, da Cunha Santos G, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol.* 2008;26(26):4268–4275.
10. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer—molecular and clinical predictors of outcome. *N Engl J Med.* 2005;353(2):133–144.
11. *Ontario Health Insurance (OHIP) Schedule of Benefits and Fees.* Toronto, ON, Canada: Ontario Ministry of Health and Long Term Care; 2007.
12. PPS Pharma Publication. *Total Pricing Systems Inc.* http://www.ppspharma.com/main.shtm. Accessed April 2007.
13. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10 Revision, Version for 2007, Code (ICD-10).* http://www.who.int/classifications/icd/en/. Accessed April 2007.
14. Ng R, Hasan B, Mittmann N, et al. Economic analysis of NCIC CTG JBR.10: a randomized trial of adjuvant vinorelbine plus cisplatin compared with observation in early stage non-small-cell lung cancer—a report of the Working Group on Economic Analysis, and the Lung Disease Site Group, National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007;25(16):2256–2261.
15. Shah NT, Kris MG, Pao W, et al. Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J Clin Oncol.* 2005;23(1):165–174.
16. Chou LS, Garey J, Oishi K, Kim E. Managing dermatologic toxicities of epidermal growth factor receptor inhibitors. *Clin Lung Cancer.* 2006;8(suppl 1):S15–S22.
17. Leighl NB, Shepherd FA, Kwong R, Burkes RL, Feld R, Goodwin PJ. Economic analysis of the TAX 317 trial: docetaxel versus best supportive care as second-line therapy of advanced non-small-cell lung cancer. *J Clin Oncol.* 2002;20(5):1344–1352.
18. Willan AR, Briggs AH. *The Statistical Analysis of Cost Effectiveness Data.* Chichester, UK: Wiley; 2006.
19. http://www.nice.org.uk/Guidance/TA162. Accessed November 29, 2008.
20. http://www.pharmac.govt.nz/patients/Schedule. Accessed December 3, 2008.
21. http://www.pharmac.govt.nz/2006/05/01/140607c.pdf. Accessed August 24, 2008.
22. http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-erlotinib-nov06. Accessed November 30, 2008.
23. www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/phase1-decision/drugmed/sbd_smd_2006_tarceva_094813-eng.php. Accessed November 30, 2008.
24. Ramsey SD, Clarke L, Kamath TV, Lubeck D. Evaluation of erlotinib in advanced non-small cell lung cancer: impact on the budget of a U.S. health insurance plan. *J Manag Care Pharm.* 2006;12(6):472–478.
25. Carlson JJ, Reyes C, Oestreicher N, Lubeck D, Ramsey SD, Veenstra DL. Comparative clinical and economic outcomes of treatments for refractory non-small cell lung cancer (NSCLC). *Lung Cancer.* 2008;61(3):405–415.
26. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet.* 2008;372(9652):1809–1818.
27. Niho S, Ichinose Y, Tamura T. Results of a randomized phase III study to compare the overall survival of gefitinib (IRESSA) versus docetaxel in Japanese patients with non-small-cell lung cancer who failed one or two chemotherapy regimens. *J Clin Oncol.* 2007;Abstract 25:LBA7509; 25(18s):387s.
28. http://www.roche.com/media/media_releases/med-cor-2008-11-07.htm. Accessed November 30, 2008.
29. Calvo E, Baselga J. Ethnic differences in response to epidermal growth factor receptor tyrosine kinase inhibitors. *J Clin Oncol.* 2006;24(14):2158–2163.
30. Carlson JJ, Garrison LP, Ramsey SD, Veenstra DL. The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer. *Value Health.* 2008;12(1):20–27.
31. http://www.medicareaustralia.gov.au/provider/pbs/drugs2/gefitinib.jsp. Accessed November 29, 2008.
32. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361(10):947–957.
33. Earle CC, Chapman RH, Baker CS, et al. Systematic overview of cost-utility assessments in oncology. *J Clin Oncol.* 2000;18(18):3302–3317.
34. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value Health.* 2004;7(5):518–528.
35. Bradbury P, Seymour L, Ng R, et al. An economic analysis of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) BR.21, a randomized trial of erlotinib versus best supportive care after cisplatin based chemotherapy in advanced non-small-cell lung cancer. *J Thorac Oncol.* 2007;2;8(suppl 4). Abstract P3-068, S707.
36. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ.* 1992;146(4):473–481.

ON, Canada). We also wish to acknowledge the investigators and patients who participated in the NCIC CTG BR.21 trial. Preliminary data from this study were presented at the12th World Conference on Lung Cancer, Seoul, Korea. September 2–6, 2007 (35).

Affiliations of authors: NCIC Clinical Trials Group, Kingston, ON, Canada (PAB, DT, LS, LZ, NM, M-ST, WKE, FAS, NBL); Division of Medical Oncology and Hematology, University Health Network, Princess Margaret Hospital and University of Toronto, Toronto, ON, Canada (PAB, RN, M-ST, FAS, NBL); Health Outcomes and PharmacoEconomic (HOPE) Research Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada (PKI, NM); Juravinski Cancer Centre at Hamilton Health Sciences and Department of Oncology, McMaster University, Hamilton, ON, Canada (WKE).